



PATENT  
Customer No. 22,852  
Attorney Docket No. 3495.0174-01

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE  
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of: )  
)  
Laurent COEN et al. ) Group Art Unit: 1632  
)  
Application No.: 09/816,467 ) Examiner: S. Chen  
)  
Filed: March 26, 2001 )  
)  
For: HYBRID PROTEINS THAT )  
MIGRATE RETROGRADELY AND )  
TRANSYNAPTICALLY INTO THE )  
CNS )

**Mail Stop Appeal Brief--Patents**  
Commissioner for Patents  
P.O. Box 1450  
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Sir:

**APPEAL BRIEF UNDER 37 C.F.R. § 1.192**

Pursuant to 37 C.F.R. § 1.192, appellants submit this Appeal Brief (in triplicate) with the requisite fee under 37 C.F.R. § 1.17(c) in response to the Examiner's Final Rejection of claims 17-19, 21-23, 34 and 35 dated June 4, 2003. Appellants filed a Notice of Appeal on November 4, 2003. Appellants submit concurrently with this Appeal Brief, a Petition Under 37 C.F.R. § 1.136(a) and the requisite fee under 37 C.F.R. § 1.17(a)(1) to extend the time for filing this brief for two months, up to and including March 4, 2004.

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**I. Real Party In Interest**

The real party in interest in the pending appeal is the assignee, Institut Pasteur, of Paris, France, by virtue of an assignment by appellants, duly recorded.

**II. Related Appeals and Interferences**

Appellants believe that the specification of this application is identical to that of U.S. Application S.N. 09/501,787. The '787 application is a continuation application of PCT/EP98/05113, and like the present application, claims priority to U.S. Provisional Application Nos. 60/055,615 and 60/065,236.

An Appeal Brief was filed in the '787 application on July 16, 2003, and a Supplemental Appeal Brief was filed January 12, 2004. There are currently no other appeals and no interferences known to the Appellants, the undersigned, or the assignee that will directly affect or be directly affected by or have a bearing on the Board's decision in this Appeal.

**III. Status Of Claims**

Upon entry of the Supplemental Amendment After Final filed February 3, 2004,<sup>1</sup> claims 17, 18, 21-23, 34, and 35 will be pending in this application. These claims are set forth in Appendix I. Claims 1-6 and 24-33 have been withdrawn from consideration as being directed to a non-elected invention.

Claims 17 and 18 stand provisionally rejected under the statutory (35 U.S.C. § 101) doctrine of double patenting. Claims 21-23 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting. Since these double patenting rejections are provisional, Appellants have requested that they be held

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<sup>1</sup> This Amendment canceled claims 1-6, 19, and 24-33 to place this application in better form for appeal.

in abeyance until allowable subject matter is identified. Claims 17, 18, 21-23, 34, and 35 stand rejected under 35 U.S.C. § 103.

#### **IV. Status Of Amendments**

Appellants submitted an Amendment Under 37 C.F.R. § 1.116 on August 29, 2003. An Advisory Action issued on October 20, 2003, indicating that the Amendment After Final was not entered.

On February 3, 2004, Appellants filed a Supplemental Amendment After Final canceling claims 1-6 and 24-33, directed to non-elected subject matter, as well as claim 19. This amendment was submitted to place this application in better form for appeal and has not been acted on by the Examiner.

#### **V. Summary Of Invention**

The *Clostridium tetani* bacteria produces a 150 kD protein known as the tetanus toxin. (Specification, p. 1.) Nerve cells, or neurons, internalize the tetanus toxin, where it exhibits its toxic effects by blocking the release of neurotransmitters, the chemical messengers of neurons. The toxin is activated by selective proteolytic enzymes in the body that cleave the inactive 150 kD protein into two disulfide-linked chains: a 50 kD light chain and a 100kD heavy chain. (*Id.*)

Scientists have also used proteolytic enzymes to study the structure of the tetanus toxin. (*Id.* at 2.) For example, the proteolytic enzyme, papain, cleaves the tetanus toxin into two fragments: the C terminal part of the heavy chain called fragment C and the complementary portion containing a fragment B linked to the light chain (fragment A) via a disulfide bond. (*Id.*) Fragment C appears to retain the transport properties of tetanus toxin, while fragment A retains the toxic properties. (*Id.* at 5, 9.) Specifically, the toxic properties of the tetanus toxin have been traced to a zinc-binding domain found between amino acids 225 and 245 of fragment A. (*Id.*)

Neurons are elongated cells comprising a cell body, dendrites, and an axon. Dendrites extend from the cell body as one or more outgrowths that subdivide into multiple threadlike, branches. The axon also extends from the cell body, usually over a longer distance, and branches at its end. Signals or impulses pass through the nervous system by moving from one neuron to another. More specifically, when a neuronal cell body is stimulated, it generates a signal that passes from the axon of one neuron to the dendrites of another at a junction called the synapse. This signal continues to pass from one neuron to another until reaching its target.

In the body, the tetanus toxin undergoes retrograde axonal transport and transynaptic transport. (*Id.* at 1-2.) Axonal retrograde transport refers to transport along the axon of a neuron. In other words, it means intraneuron transport, or transport within a neuron. (*Id.* at 12.) On the other hand, transynaptic transport refers to interneuron transport, or transport between different neurons and, therefore, involves transport across the synaptic junction between neurons. (*Id.* at 13.)

The pending claims are directed to tetanus toxin fragments. These tetanus toxin fragments are capable of delivering polypeptides and polynucleotides into the central nervous system. Specifically, the tetanus toxin fragments are capable of transferring *in vivo* a protein, peptide, or a polynucleotide through a neuromuscular junction and at least one synapse. (*Id.* at 4.) In other words, the tetanus toxin fragments are capable of both retrograde axonal transport and transynaptic transport. (*Id.* at 12-13.)

Claims 17 and 18 are the only independent claims. In claim 17, the hybrid fragment of tetanus toxin comprises fragment C and fragment B or at least 11 amino acid residues of fragment B. Claim 18 is like claim 17 except it recites that the hybrid tetanus toxin fragment further comprises a fraction of a fragment A devoid of its toxic

activity corresponding to the proteolytic domain having a zinc-binding motif located in the central part of the chain between amino acids 225 and 245.

Claim 21 is directed to a composition containing an active molecule in association with the hybrid fragment of tetanus toxin according to claim 17. Claim 22 depends from claim 21 and recites a list of active molecules. Claim 23 depends from claim 21 and specifies that the active molecule is a polynucleotide encoding a protein. In claim 34, which depends from claim 23, the polynucleotide further comprises a promoter capable of expression in neurons. And in claim 35, the polynucleotide further comprises an enhancer.

#### **VI. Issues**

The sole issue on appeal is whether the Examiner properly rejected claims 17, 18, 21-23, 34, and 35 under 35 U.S.C. § 103(a) as obvious over Mueller in view of Hohne-Zell et al.

#### **VII. Grouping Of Claims**

Pursuant to 37 C.F.R. § 1.192(c)(7), appellants acknowledge that claims 17, 18, 21-23, 34, and 35 stand or fall together in relation to the Examiner's 35 U.S.C. § 103 rejection.

#### **VIII. Argument**

**Claims 17, 18, 21-23, 34, and 35 are not obvious under 35 U.S.C. § 103(a) over Mueller in view of Hohne-Zell et al.**

In the Final Office Action, the Examiner rejected claims 17-18, 21-23 and 34-35 under 35 U.S.C. § 103(a) as allegedly being obvious over Mueller, 1994 (Report, ARO-27890.1-LS, Order No. AD-A290 501, NTIS, p. 1-15) in view of Hohne-Zell et al., 1993 FEBS Letters, Vol. 336, No. 1, p. 175-180. (Paper No. 14, pp. 8-9.) The Examiner maintained this rejection in an Advisory Action dated October 20, 2003. Appellants

respectfully submit that this 35 U.S.C. § 103(a) rejection is improper because the cited references, Mueller and Hohne-Zell et al., fail to teach or suggest all elements of the claimed invention. Furthermore, even assuming Mueller and Hohne-Zell et al. did teach every element of the claimed invention, there is no motivation to combine the two references.

**A. Mueller fails to teach or suggest a hybrid tetanus toxin fragment having fragment B, or a fraction thereof having at least 11 amino acid residues.**

Claims 17 and 18 recite a hybrid tetanus toxin fragment comprising a fragment C and a fragment B, or a fraction of fragment B having at least 11 amino acid residues. The remaining claims depend directly or indirectly from claims 17 or 18. Mueller does not teach or suggest a hybrid tetanus toxin **fragment** that includes fragment B, or a fraction thereof having at least 11 amino acid residues. Indeed, even the Examiner has acknowledged that “Mueller does not teach a hybrid fragment comprising fragment C of tetanus toxin and at least 11 amino acid residues of fragment B . . . .” (Paper No. 11, p. 10.)

Mueller studied receptor-mediated gene transfer in the central nervous system. More specifically, Mueller investigated whether wheat germ agglutinin or fragment C of tetanus toxin could be used to introduce foreign genes into nerve cells. (See, e.g., Abstract on Report Documentation Page.) Mueller found that “receptor-mediated uptake [was] not an efficient means for directing the expression of foreign genes in nerve cells *in vivo*.” (*Id.*)

**1. Mueller’s discussion of the well-known properties of the tetanus toxin do not render the claimed invention obvious.**

As part of the background, Mueller explains that tetanus toxin is a well-characterized protein that is known to be internalized by neurons through receptor-

mediated endocytosis. (*Id.* at 3.) Mueller further explains that once the neurons internalize the tetanus toxin, the toxin is transported retrogradely to the neuronal cell bodies. (*Id.*) The Examiner relies on this background information from Mueller for teaching that neurons internalize the tetanus toxin, permitting the transfer of tetanus toxin from the blood into the central nervous system. (Paper No. 14, p. 8.) This property of the tetanus toxin, however, is well known, as explained in Appellants' own specification. (See, e.g., Specification, pp. 2, 8.) Nevertheless, because Mueller discusses the neuronal transport properties of the full tetanus toxin protein, which contains fragments A, B, and C, the Examiner infers that the reference necessarily teaches the use of a tetanus toxin that includes fragments B and C. Specifically, the Examiner asserts that

Mueller teaches receptor mediated gene transfer in the central nervous system and "tetanus toxin is uniquely specific for uptake into neurons and enters the central nervous system from the circulation with the highest efficiency of any known protein." (e.g. p. 3). Tetanus toxin includes fragment B and C, and contains at least 11 amino acid residues of fragment [sic, fragment] B. Thus, Mueller implies the use of tetanus toxin that includes fragment B and fragment C for receptor mediated gene transfer in the central nervous system.

(Paper No. 14, p. 8.)

**a. The Examiner ignores the "fragment" element of the claimed invention.**

Relying on the open transitional phrase "comprising" in the claims, the Examiner takes the position that "the claims include using the whole tetanus toxin." (Advisory Action, p. 2.) The Examiner's position, however, ignores express recitations in the claims, which are directed to "a hybrid **fragment** of tetanus toxin."



**b. The term “fragment” appears in both the preamble and body of the claims and gives meaning to the claims.**

This “fragment” recitation appears not only in the preamble of claims 17 and 18 but also in the body of both these claims. Specifically, both claims 17 and 18 recite:

A hybrid fragment of tetanus toxin comprising . . . wherein **the hybrid fragment** is capable of transferring in vivo a protein, a peptide, or a polynucleotide through a neuromuscular junction and at least one synapse.

Thus, “the hybrid fragment” is recited in the body of the claim and is a necessary element of the claimed invention. As set forth in Section 2111.02 of the M.P.E.P.:

“[A] claim preamble has the import that the claim as a whole suggests for it.” *Bell Communications Research, Inc. v. Vitalink Communications Corp.*, 55 F.3d 615, 620, 34 USPQ2d 1816, 1820 (Fed. Cir. 1995). “If the claim preamble, when read in the context of the entire claim, recites limitations of the claim, or, if the claim preamble is ‘necessary to give life, meaning, and vitality’ to the claim, then the claim preamble should be construed as if in the balance of the claim.” *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305, 51 USPQ2d 1161, 1165-66 (Fed. Cir. 1999).

Here, when reading the preamble in the context of the entire claim, it is evident that the “hybrid fragment” is a necessary element of the claim. Indeed, it is an element that reappears in the body of the claim and, therefore, is “necessary to give life, meaning and vitality to the claim.” *Pitney Bowes*, 182 F.3d at 1305, 51 USPQ2d at 1165-66.

**c. The term fragment provides structural information about the claimed invention.**

Furthermore, the term “fragment” provides a structural element to the claimed invention. The claims are directed to hybrid fragments of tetanus toxin. By its very

definition,<sup>2</sup> the term fragment connotes some portion less than the whole, in this case some portion less than the whole tetanus toxin. As set forth in the M.P.E.P., if terminology in the preamble affects the structure of the claimed invention, “it must be treated as a claim limitation.” M.P.E.P. § 2111.02; *see, e.g., Corning Glass Works v. Sumitomo Elec. U.S.A., Inc.*, 868 F.2d 1251, 1257, 9 USPQ2d 1962, 1966 (Fed. Cir. 1989). Moreover, determining whether a preamble recitation is a structural element “can be resolved only on review of the entirety of the application ‘to gain an understanding of what the inventors actually invented and intended to encompass by the claim.’” M.P.E.P. § 211.02 (citing *Pac-Tec Inc. v. Amerace Corp.*, 903 F.2d 796, 801, 14 USPQ2d 1871, 1876 (Fed. Cir. 1990)).

Here, the specification makes clear that the invention is directed to fragments of tetanus toxin. For example, the first paragraph of the specification explains:

This invention relates to the use of **part** of tetanus toxin for delivering a composition to the central nervous system of a human or animal. This invention also relates to a hybrid **fragment** of tetanus toxin, a polynucleotide that hybridizes with natural tetanus toxin, and a composition containing the tetanus toxin **fragment** as an active molecule. Further, this invention relates to a vector comprising a promoter and a nucleic acid sequence encoding the tetanus toxin **fragment**.

(Specification, p. 1; emphasis added.) The Summary of the invention further explains that this invention provides, *inter alia*,

a method for *in vivo* delivery of desired composition into the central nervous system (CNS) of the mammal, wherein the composition comprises a non-toxic, proteolytic **fragment** of tetanus toxin (TT) in association with at least a molecule having a biological function[;]

\* \* \*

a hybrid **fragment** of tetanus toxin[;]

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<sup>2</sup> American Heritage dictionary defines fragment as “an incomplete or isolated portion; bit.”

\* \* \*

a composition comprising an active molecule in association with the hybrid **fragment** of tetanus toxin (TT)[; and]

\* \* \*

a vector comprising . . . a nucleic acid coding for the **fragment** of tetanus toxin of the invention . . .

(Specification. pp. 4-7; emphasis added.) And the specification clearly distinguishes between the whole tetanus toxin and the tetanus toxin fragments of the present invention. (See, e.g., Specification, pp. 2-4.)

Appellants have maintained this distinction in the claims by using the term “fragment” in both the preamble and body of independent claims 17 and 18. The Examiner cannot ignore this element of the claimed invention when comparing the claimed invention to the prior art. Therefore, contrary to the Examiner’s assertions, the teachings in Mueller about the known and well-characterized properties of the tetanus toxin do not teach or suggest Appellants’ claimed tetanus toxin fragments or compositions containing the same. Thus, Mueller fails to teach or suggest every element of the claimed invention.

**2. Mueller teaches away from the claimed invention by physically removing fragment B from the tetanus toxin constructs used in his gene transfer study.**

Furthermore, Mueller teaches away from the claimed invention. Specifically, Mueller teaches using only fragment C in his gene transfer study and in the process of preparing fragment C, Mueller actually **removes** fragment B. As shown in Mueller, proteolytic digestion of tetanus toxin yields two parts: fragment C and a fragment B containing portion, which includes fragment B linked to the light chain by a disulfide

bond. (Mueller, p. 3, Figure 1.)<sup>3</sup> Mueller recognizes that fragment C is not toxic, “yet it is sufficient for internalization and transport, and therefore could be safely utilized as a carrier molecule for neuron specific gene transfer *in vivo*.” (*Id.* at 4.) Therefore, Mueller “hypothesized that genes complexed to the **C-fragment** of tetanus toxin will be taken up efficiently and specifically by neurons.” (*Id.*; emphasis added.) Accordingly, Mueller set out to separate and purify fragment C from the remainder of the natural tetanus toxin (including fragment B). (*Id.* at 3, Figure 1.)

Specifically, Mueller prepared fragment C by digesting the tetanus toxin with the proteolytic enzyme, trypsin. This digestion produced two tetanus toxin portions: the “cell binding (C-fragment) and cytotoxic (B-fragment) portions” depicted in Figure 1. (*Id.* at 4.) The non-toxic fragment C obtained from the proteolytic digest was purified by either gel filtration or fast protein liquid chromatography. The purified fragment C was then attached to polylysine, “which serves as a bridge for the non-covalent, electrostatic binding of negatively charged DNA.” (Mueller, p. 4, see *also*, Figure 3.)

Mueller never mentions adding fragment B, or a fraction thereof, to the purified fragment C. In fact, in the process of purifying fragment C, Mueller specifically teaches separating fragment C from fragment B and getting rid of the latter. Mueller demonstrates that a skilled artisan would be motivated to exclude fragment B from a tetanus toxin fragment for use in gene transfer studies, because fragment C alone was believed to be sufficient for the transport properties of the natural tetanus toxin and because fragment C could be readily obtained by separating it from the remainder of the

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<sup>3</sup> The disulfide bond linking fragment B to the light chain is represented in Figure 1 by the designation “-S-S-” This arrangement is similarly described in Appellants’ specification, which explains that papain cleaves tetanus toxin into fragment C and a second portion containing “fragment B linked to the light chain (fragment A) via a disulfide bond.” (Specification, p. 2.)

tetanus toxin (including fragment B) through known proteolytic digestion methods.

Mueller, therefore, teaches away from the claimed invention.

**B. Hohne-Zell et al. fail to teach or suggest a hybrid tetanus toxin fragment having fragment B, or a fraction thereof having at least 11 amino acid residues.**

Hohne-Zell et al. fail to remedy the deficiencies of Mueller. Hohne-Zell et al. generated and analyzed mutant tetanus toxin light chains to determine whether they could retain the ability of the wild type light chain to block the release of neurotransmitters. (Hohne-Zell et al., p. 176, first column.) As discussed previously, tetanus toxin exhibits its toxic effect by blocking the release of neurotransmitters in nerve cells. The toxic activity resides in the light chain (or fragment A)<sup>4</sup> of tetanus toxin. Using mutant fragment A constructs, Hohne-Zell et al. demonstrated that certain mutations within the zinc-binding domain of fragment A (i.e., positions 233 and 234) abolish the ability of fragment A to block neurotransmitter release. In other words, the toxic activity of tetanus toxin is found in the zinc-binding domain of fragment A.<sup>5</sup> Therefore, Hohne-Zell et al. studied recombinant tetanus toxin light chains (i.e., fragment A of tetanus toxin). Hohne-Zell et al. do not disclose, or suggest, a tetanus toxin fragment containing fragment C and fragment B.

Thus, the cited references, Mueller and Hohne-Zell et al., fail to teach or suggest all elements of the claimed invention. Accordingly, Appellants respectfully request reversal of this 35 U.S.C. § 103 rejection.

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<sup>4</sup> See, e.g., Specification, p. 2 ("the other part contained fragment B linked to the light chain (fragment A) via a disulfide bond.")

<sup>5</sup> This property of tetanus toxin is noted in the specification, which describes one embodiment of the invention as a tetanus toxin fragment containing, *inter alia*, "a fraction of a fragment A devoid of its toxic activity corresponding to the proteolytic domain having a zinc-binding motif located in the central part of the chain between the amino acids 225 and 245 . . . ." (Specification, p. 9.) This recitation can be found in claim 18.

**C. There is no motivation to combine the teachings of Mueller and Hohne-Zell et al.**

As discussed above, Mueller and Hohne-Zell et al. fail to teach every element of the claimed invention. However, even assuming that the two references, when combined, taught every element of the claimed invention, there would still be no *prima facie* case of obviousness.

Obviousness must be determined with respect to the invention as a whole. “[T]he inquiry is not whether each element existed in the prior art, but whether the prior art made obvious the invention as a whole for which patentability is claimed.” *Hartness Int’l, Inc. v. Simplimatic Eng’g Co.*, 819 F.2d 1100, 1108, 2 USPQ2d 1826, 1832 (Fed. Cir. 1987). Furthermore, to establish obviousness based on a combination of elements disclosed in the prior art, the Office must demonstrate a motivation, suggestion, or teaching of the desirability of making the specific combination that the applicants made. *In re Kotzab*, 217 F.3d 1365, 1369, 55 USPQ2d 1313, 1316 (Fed. Cir. 2000) (reversing the Board’s 35 U.S.C. § 103 rejection because there was no motivation to combine the references). The motivation to combine the references may derive from statements in the references, the knowledge of one of skill in the art, or even the nature of the problem to be solved. *Id.* at 1370, 55 USPQ2d at 1317. Here, no such motivation exists.

“The factual inquiry whether to combine references must be thorough and searching.” *In re Lee*, 277 F.3d at 1343, 61 USPQ2d at 1433 (quoting *McGinley v. Franklin Sports, Inc.*, 262 F.3d 1339, 1351-52, 60 USPQ2d 1001, 1008 (Fed. Cir. 2001)). *See also, Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1334, 63 USPQ2d 1374, 1387 (Fed. Cir. 2002) (“The showing of a motivation to combine must be clear and particular, and it must be supported by actual evidence.”)

Here, because Hohne-Zell et al. teach that the toxic properties of tetanus toxin reside in the putative zinc-binding domain of fragment A, the Examiner summarily concludes that “it would have been obvious for one of ordinary skill at the time of the invention to generate the claimed hybrid fragment or composition devoid of the zinc-binding domain to remove TT toxic activity for neuron specific gene transfer to central nervous system according to the collective teachings of Mueller and Hohne-Zell.” (Paper No. 14, p. 9.) However, “[b]road conclusory statements regarding the teachings of multiple references, standing alone, are not ‘evidence.’” *In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999). Therefore, the Examiner’s conclusory statement about generating the claimed hybrid fragments does not provide the clear and particular evidence required to establish the motivation to combine references under 35 U.S.C. § 103.

Furthermore, as discussed above, Mueller teaches discarding fragment B and retaining only fragment C for gene transfer experiments. Hohne-Zell et al. teach that fragment A is toxic, and the Examiner appears to conclude that one would, therefore, exclude fragment A. If fragment B (Mueller) and fragment A (Hohne-Zell et al.) are removed from the tetanus toxin, only fragment C remains. This is not Appellants’ claimed invention. Thus, there is no suggestion or motivation to modify the teachings of Mueller and Hohne-Zell et al. to produce the claimed fragments and compositions.

For this additional reason, Appellants respectfully request reversal of this 35 U.S.C. § 103 rejection.

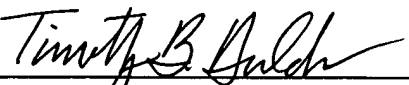
To the extent any further extension of time under 37 C.F.R. § 1.136 is required to obtain entry of this Appeal Brief, such extension is hereby respectfully requested. If there are any fees due under 37 C.F.R. §§ 1.16 or 1.17 which are not enclosed

herewith, including any fees required for an extension of time under 37 C.F.R. § 1.136,  
please charge such fees to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,  
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Dated: March 1, 2004

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## Appendix I

### Claims on Appeal

17. A hybrid fragment of tetanus toxin comprising a fragment C and a fragment B or a fraction of fragment B having at least 11 amino acid residues, wherein the hybrid fragment is capable of transferring *in vivo* a protein, a peptide, or a polynucleotide through a neuromuscular junction and at least one synapse.

18. A hybrid fragment of tetanus toxin comprising a fragment C and a fragment B or a fraction of fragment B having at least 11 amino acid residues and a fraction of a fragment A devoid of its toxic activity corresponding to the proteolytic domain having a zinc-binding motif located in the central part of the chain between amino acids 225 and 245, wherein the hybrid fragment is capable of transferring *in vivo* a protein, a peptide or a polynucleotide through a neuromuscular junction and at least one synapse.

21. A composition containing an active molecule in association with a hybrid fragment of tetanus toxin according to claim 17.

22. The composition according to claim 21, wherein the active molecule is selected from the group consisting of protein SMN, BDNF (brain-derived neurotrophic factor), NT-3, NT-4/5, GDNF (Glial cell-line derived neurotrophic factor), IGF (Insulin-like growth factor), PNI (protease nexin I), SP13 (Serine Protease Inhibitor protein), ICE, Bcl-2, GFP (green fluorescent protein), endonucleases like I-SceI or CRE, antibodies or drugs specifically directed against neurodegenerative diseases such as latero spinal amyotrophy (LSA).

23. The composition according to claim 21, wherein the active molecule is a polynucleotide encoding a protein.

34. The composition according to claim 23, wherein the polynucleotide further comprises a promoter capable of expression in neurons.

35. The composition according to claim 34, wherein the polynucleotide further comprises an enhancer.